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Case study

An 8-year old boy with continuous spikes and waves during slow sleep presenting with positive onconeuronal antibodies

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ABSTRACT

Objective: To determine the etiology of epilepsy with continuous spikes and waves during slow sleep (CSWS)/electrical status epilepticus during sleep (ESES) in an 8-year old boy with a history of neuroblastoma and opsoclonus-myoclonus.

Material & methods: A combination of clinical characterization and follow-up, video EEG and laboratory investigations.

Results: We report the case of an 8-year old boy with a history of neuroblastoma and opsoclonus-myoclonus, who presented with intellectual disability, pharmacotherapy-resistant epilepsy and CSWS/ESES. Although the patient's neuroblastoma had been successfully treated 8 years prior to presentation and an extensive workup did not show a tumor reoccurrence, testing for onconeuronal antibodies was positive for anti-Ma2 and anti-CV2/CRMP5 antibodies. High-dose intravenous methylprednisolone and a taper of oral methylprednisolone were given, leading to a significant clinical improvement. During the taper the patient's condition and EEG manifestations deteriorated again necessitating another cycle of steroid therapy, which lead to a stable improvement. During a 6-month follow-up no CSWS/ESES was seen on EEG and anti-Ma2 and anti-CV2/CRMP5 antibodies remained undetectable.

Conclusion: This case suggests that onconeuronal antibodies may be involved in the pathogenesis of CSWS/ESES.

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1. Introduction

Continues spikes and waves during sleep (CSWS) is a rare epileptic encephalopathy of childhood characterized by seizures, an electroencephalographic pattern of electrical status epilepticus during sleep (ESES) and neurocognitive regression. CWS is difficult to treat and the response to conventional antiepileptic drugs is often incomplete and transitory. The etiology of CSWS is often unclear with many cases being classified as cryptogenic. Known causes include early developmental lesions such as vascular lesions of the thalamic regions or malformations of cortical development such as polymicrogyria. These abnormalities may disturb the corticothalamocortical neuronal network and lead to generalize spikes and waves. Recently, mutations in the GRIN2A gene, encoding a subunit of the NMDA receptor, were identified as a risk factor for CSWS. An underlying immune disorder has also been proposed as an etiology for certain cases of idiopathic CSWS/ESES, and is supported by the successful application of immunosuppressive treatment with corticosteroids or immunoglobulins.[1] Recently, the detection of autoantibodies in unexplained epilepsies reinforced a potential causal link of immunity and inflammation in epilepsies of unknown etiology.[2] Nevertheless, it remains unclear whether neuroautoantibodies exist in epilepsy with CSWS/ESES syndrome. Here, we describe the case of an 8-year old boy with a history of neuroblastoma and opsoclonus myoclonus syndrome (OMS) that presented with pharmacotherapy-resistant epilepsy with CSWS/ESES and showed anti-Ma2 and anti-CV2/CRMP5 antibodies.

2. Case study

This 8-year old boy presented with bilateral strabismus during the neonatal period and at five months of age an abdominal mass was accidentally palpated. Abdominal ultrasound and CT scan showed a mass on the left adrenal gland and he was referred for surgical removal of the mass. Pathology of resected mass demonstrated neuroblastoma and he was diagnosed with neuroblastoma and OMS. He subsequently underwent chemotherapy for six months. The strabismus disappeared and no relapse occurred during the follow-up period. At the age of 2.5 years, he experienced unprovoked convulsions while asleep with twitching of the left muscle around the mouth and the eyes lasting several seconds. Seizures gradually worsened over the following two years. At the age of 4.5 years, he was referred to a pediatrician for the first time. EEG showed sharp waves and sharp-wave complexes during sleep over the central lobes and parietotemporal regions bilaterally. Brain MRI showed a slight enlargement of left lateral ventricle compared to the right. He was diagnosed with “epilepsy” and was given valproic acid (VPA), which relieved the convulsions. However, after 16 months of treatment with VPA and although blood levels were within the therapeutic range, convulsions resurfaced and were again clinically evident in the form of twitching movements of the cheilion and canthus muscles during sleep. Meanwhile, limb tremor occurred, psychomotor regression ensued, and the patient was referred to a neuropediatrician. Lamotrigine (LTG) was prescribed, and the convulsions apparently decreased in frequency. However, limb tremor remained so severe that he was unable to eat by himself. Owing to continuing deterioration and severe developmental retardation, the patient was referred to our clinic at the age of 8 years and 5 months (Table 1).

The patient is the firstborn son of healthy, unrelated parents of Han origin. Family history was negative for epilepsy. He was born at term after a normal pregnancy, and was pronounced healthy as appropriate for gestational age. The delivery and postnatal period were uneventful. His early development revealed the following deficits: He learned to walk independently at the age of 1.5 years but had poor balance, was unable to walk straight, and fell easily. Moreover, he was unable to jump, run, count, and distinguish colors while showing hyperactivity, irritability, sialorrhea, dysfluency, constipation, and poor appetite.

Neurological examination revealed normal muscle strength, tone, deep tendon reflexes, and sensations. Mild truncal ataxia, intention tremor, and dysdiadachokinesia were observed, along with intermittent limb tremor. No neck stiffness was present.

Video-EEG demonstrated continues bilateral central, parietal, and middle-posterior temporal epileptic activity, and the spike-and-waves complex index during sleep exceeded 85% (Fig. 1 EEG-A). Laboratory tests including complete blood count, glucose, electrolytes and liver and kidney function tests were within normal limits. Brain MRI showed a minimal enlargement of the left lateral ventricle along with the presentation of mild encephalatrophy. PET/CT showed no abnormal metabolism (Supplementary Fig. 1). Cytological analysis of bone marrow (BM) showed no abnormal findings. ECT scan of the bone showed no osseous metastasis. The flow cytometry (FCM) detection of minimal residual disease (MRD) in BM showed that 0.05% karyocytes expressed CD19, CD181bri, CD56, and HLA-ABCdim but not CK and CD45 (Supplementary Fig. 2 FCM-A). An onconeuronal antibody test revealed anti-Ma2 and anti-CV2/CRMP5 autoantibodies.

Thus, based on the clinical manifestation, the results of work-up, and the history of neuroblastoma for 8 years, the patient was diagnosed with epilepsy with CSWS/ESES of potential paraneoplastic origin given the presence of antineuronal antibodies. A methylprednisolone pulse (20 mg/kg/d for 3 days, then 10 mg/kg/d for 3 days, 5 mg/kg/d for 3 days) was given and was followed by an oral methylprednisolone taper (1 mg/kg/d). VPA was continued and LTG was gradually replaced with levetiracetam (LEV). A clinical response was seen on the third day of the methylprednisolone pulse. The frequency of limb tremor decreased, sialorrhea and anorthopia were alleviated, and appetite took a favorable turn. Two months later, video-EEG still demonstrated bilateral central, parietal, and middle-posterior temporal continuous epileptic activity along with a spike-and-waves complex index of more than 75% during sleep. In summary, the patient's clinical symptoms significantly alleviated with limb tremor, sialorrhea and visible seizures disappearing, and his speech became more fluent (repetitive language still existed). He was able to count from 1 to 90 correctly, his balance improved significantly, but he still could not walk straight, jump or run, and mild heterotropia remained. In the following period, oral

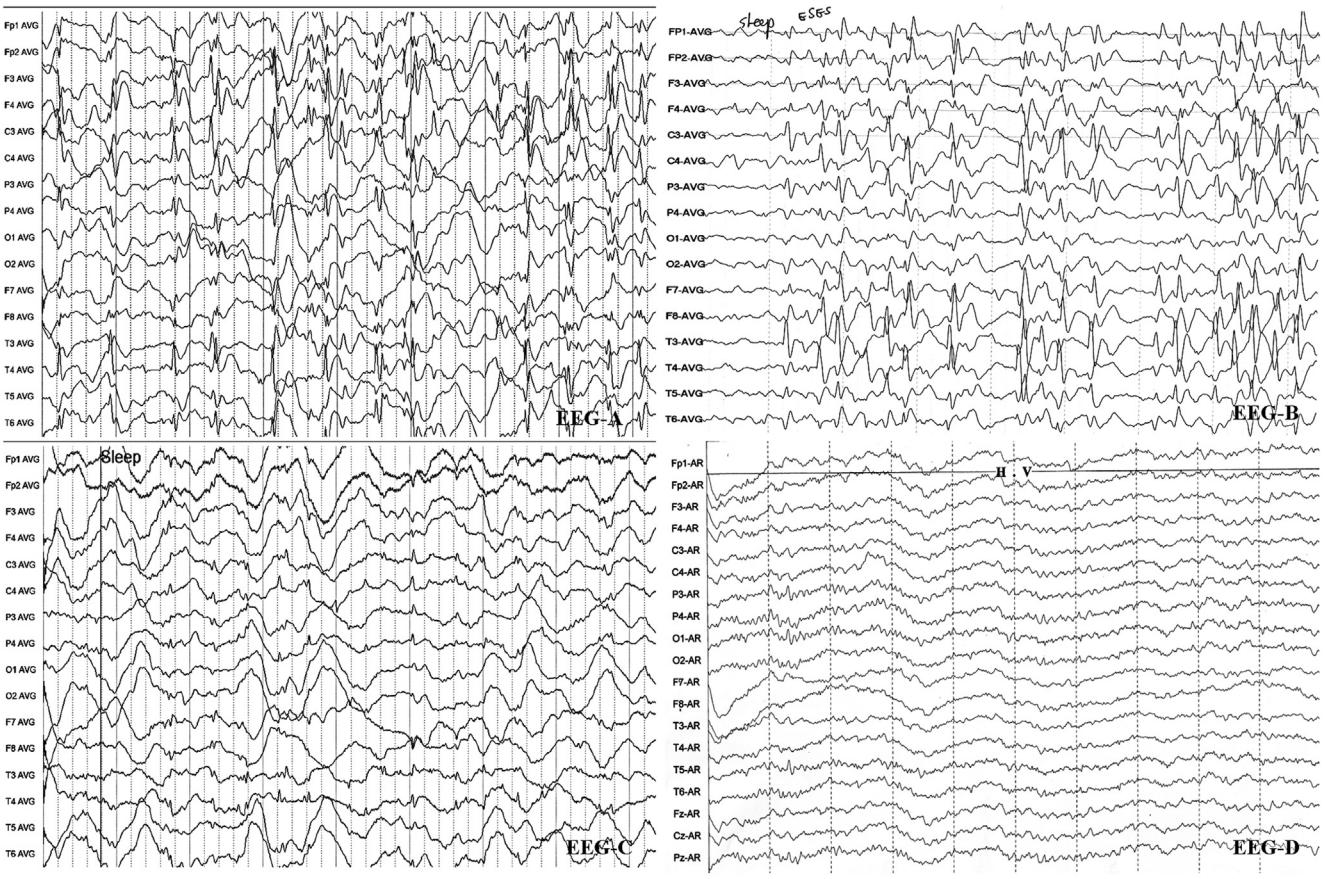

Fig. 1 – The EEG before and after treatment: EEG-A. The EEG before treatment: bilateral central, parietal and middle-posterior temporal continuous epileptic activity, spike-and-waves complex index exceeded 85% during sleep (Continuous Spikes And Waves During Slow Sleep/Electrical Status Epilepticus During Sleep, CSWS/ESES); EEG-B. The EEG at 2 months after oral methylprednisolone decreased: continuous bilateral central, parietal, and middle-posterior temporal epileptic activity, and the spike-and-waves complex index was higher than 75% during sleep, CSWS/ESES still existed; EEG-C. The EEG after the second methylprednisolone pulse treatment: EEG shows no signs of CSWS/ESES although epileptic activity is still present; EEG-D. EEG 3-months after the second methylprednisolone pulse treatment shows no epileptic activity.

methylprednisolone was gradually decreased until after two months, seizures during sleep, limb tremor, and sialorrhea reoccurred and video-EEG demonstrated ESES again (Fig. 1 EEG-B). Moreover, onconeuronal antibodies testing showed anti-Ma2 and anti-CV2/CRMP5 antibodies and FCM detection of MRD in BM was negative (Supplementary Fig. 2 FCM-B). The patient underwent another methylprednisolone pulse and was maintained on oral methylprednisolone. After this second methylprednisolone pulse, not only did the clinical signs significantly relieve, but video-EEG confirmed that ESES disappeared despite residual epileptic activity (Fig. 1 EEG-C). One month later, sleep EEG showed no epileptic activity which was confirmed over an additional 6-month follow-up. At age 9-years, EEG is normal during wakefulness and sleep (Fig. 1 EEG-D) and onconeuronal antibodies are not detectable (Table 1).

3. Discussion

In our previous study, LEV was identified to be effective in individuals with ESES.[3] Considering that LTG could aggravate limb tremor, LTG was discontinued and at the same time, LEV was added to replace LTG. After methylprednisolone was introduced, the symptoms quickly ameliorated. However, the boy experienced a relapse as methylprednisolone was tapered. Convulsions reappeared and EEG showed CSWS/ESES again. Another methylprednisolone pulse resulted in a significant improvement with CSWS/ESES disappearing and EEG returning to normal. Thus in the present case, not LTG's withdrawal and LEV's add-on but methylprednisolone likely played a key role in controlling the patient's condition. Although a causal link between onconeuronal antibodies and CSWS/ESES in this case remains to be established, the successful treatment with high dose methylprednisolone does support an immunological etiology. This is corroborated by a study by Boscoloa et al. that demonstrated anti-brain autoantibodies in patients with Landau-Kleffner syndrome, benign epilepsy of childhood with rolandic spikes and CSWS syndrome.[4] Our case strengthens the hypothesis that at least in a subset of patients, an autoimmune mechanism might be involved in the pathogenesis of the CSWS/ESES Table 1.

Moreover, autoimmune etiology is identified most readily in patients with epilepsy who have a history of neoplasia in the preceding 5 years.[5] In the present case, the boy had been

Table 1 – The course of the disease.

Age	Symptoms	Work up	Diagnosis	Treatment	Outcome
6 months	Bilateral strabismus Abdominal mass Developmental delay	Abdominal ultrasound CT scan Biopsy	Neuroblastoma OMS	Surgical resection Chemotherapy for 6 months	OMS disappeared Developmental milestones delayed
2.5 years	Seizures during sleep Developmental delay	Did not see doctor			
4.5 years	Seizures worsened Developmental delay	EEG	Epilepsy	VPA	Seizures decreased Developmental delay
5 years 10 months	Clinical seizures reappeared Limb tremor evolved Intellectual disability (moderate)	None	Epilepsy	VPA + LTG	Seizures decreased Limb tremor remained Intellectual disability (moderate)
8 years 5 months	Convulsions during sleep worsened Limb tremor worsened Intellectual disability (severe)	EEG Brain MRI; PET/CT; ECT scan FCM detection of MRD positive Onconeuronal Ab positive	CSWS/ESES PNS	High-dose iv methylprednisolone pulse Oral methylprednisolone for maintenance LTG discontinued, LEV added	Symptoms improved Intellectual disability (moderate)
8 years 8 months	Convulsions disappeared Limb tremor disappeared Intellectual disability (moderate)			Oral methylprednisolone decreased	
8 years 10 months	Seizures during sleep, limb tremor developed again Intellectual disability (severe)	EEG FCM detection of MRD negative Onconeuronal Ab positive	CSWS/ESES PNS	High-dose iv methylprednisolone pulse Oral methylprednisolone for maintenance VPA + LEV	Symptoms alleviated Intellectual disability (moderate)
9 years	No seizures, no limb tremor Intellectual disability (moderate)	EEG Onconeuronal Ab negative		Oral methylprednisolone for maintenance VPA + LEV	No CSWS/ESES EEG normal
9 years 2 months	No seizures, no limb tremor Intellectual disability (moderate)	EEG		Oral methylprednisolone for maintenance VPA + LEV	Intellectual disability (moderate)

Abbreviations: OMS: Opsoclonus myoclonus syndrome; VPA: valproic acid; LTG: lamotrigine; LEV: levetiracetam; FCM: Flow cytometry; MRD: minimal residual disease; BM: bone marrow; Ab: antibody; CSWS: continuous spikes and waves during slow sleep; ESES: electrical status epilepticus in slow sleep; PNS: paraneoplastic syndrome.

diagnosed with neuroblastoma and OMS for 8 years and onconeuronal antibodies were positive. Moreover, after methylprednisolone treatment, his symptoms ameliorated dramatically supporting that, in this case, epilepsy with CSWS/ESES may be associated with onconeuronal antibodies. In general, the antibodies that are likely pathogenic are directed against cell surface antigens. These antineuronal antibodies interfere with neuronal signaling or synaptic transmission. In contrast, when antibodies are directed against intracellular antigens, such as anti-Ma2 and anti-CV2/CRMP, the pathogenic mechanism for neuronal damage appears to be mediated by cytotoxic T cells.[6]

Although we can't confirm whether autoantibodies play a causal role in our case or are simply a coincidence, we argue that the association between ESES/CSWS and onconeuronal antibodies deserves further attention.

Conflict of interest statement

Nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejpn.2014.12.012.

REFERENCES

1. Nickels K, Wirrell E. FRCPC. Electrical status epilepticus in sleep. *Semin Pediatr Neurol* 2008;**15**:50–60.
2. Nabbout R. Autoimmune and inflammatory epilepsies. *Epilepsia* 2012;**53**:58–62.
3. Chen XQ, Zhang WN, Yang ZX, Zhao M, Cai FC, Huang SP, Gao L, Pang BD, Chen X, Zou LP. Efficacy of levetiracetam in electrical status epilepticus during sleep of children: a multicenter experience. *Pediatr Neurol* 2013;**3**:1–7.
4. Boscoloa S, Baldasb V, Gobbic G, Giordanod L, Cionie G, Notb T, Venturab A, Tongiorgi E. Anti-brain but not celiac disease antibodies in Landau-Kleffner syndrome and related epilepsies. *J Neuroimmunol* 2005;**160**:228–32.
5. Bien CG, Elger CE. Limbic encephalitis: a cause of temporal lobe epilepsy with onset in adult life. *Epilepsy Behav* 2007;**10**:529–38.
6. Rosenfeld MR, Dalmau J. Update on paraneoplastic neurologic disorders. *Oncol* 2010;**15**:603–17.